

EDITORIAL

Chemical plant protection.
Past. Present. Future?

Moore's Law: the number of transistors in a dense integrated circuit doubles approximately every two years (Moore, 1965).

Eroom's Law (spelled as Moore's Law spelled backwards): drug discovery is slowing down and the cost of developing a new drug doubles every nine years (Scanwell *et al.*, 2012).

After the discovery (1938) and huge commercial and popular success of the insecticide DDT (Figure 1, Nobel Prize for its discoverer Paul Müller in 1948) a number of chemical companies started to develop new pesticide active ingredients. The demand for such chemicals was high: they were inexpensive and highly efficient replacements for earlier labor-intensive crop protection practices. As a result, the number of newly developed pesticides increased continuously and their use spread out to almost all areas of human activities from household crop production to households, forestry, food storage, *etc.*

This upward curve was broken suddenly by an alarming number of reports published on the negative effects of pesticides on human health and the environment (summarized by Rachel Carson in her exceptionally influential book "Silent Spring") (Carson, 1962). As a consequence, DDT was banned (first by Hungary in 1968) and increasingly higher standards of pest control ability and environmental toxicity were demanded by the regulatory agencies for the registration and use of pesticides (Matthews, 2015).

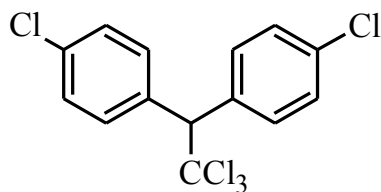


Figure 1. The chemical structure of DDT.

As a matter of fact, pesticide research and development (R&D) has been at the crossroads ever since then. Pesticide producers had to realize that commercial success is more and more difficult to achieve and the R&D methods used earlier (based on trial and error: testing random chemicals for phenotypic pesticidal effects) are not satisfactory any longer. In a bold move, the agrochemical giant Monsanto shifted away from the chemical approach in 1981 and set biotechnology as the company's strategic research focus. At the same time, for the companies that remained in the agrochemical arena, R&D costs of new pesticide active ingredients increased dramatically (similarly to pharmaceuticals: *cf.* Eroom's Law), and the success rate to find a marketable one dropped sharply. Companies responded by increasing their R&D expenditures, introduced combinatorial chemistry to generate a larger number of test compounds and applied high-throughput screening to detect phenotypic responses.

In the practice of plant protection pesticides remained indispensable but more and more efforts were taken to apply them in the framework of integrated pest management (IPM). IPM was formulated in 1972 on the prevention, monitoring and rapid identification of the pest(s) and disease(s) and their effective control by a coordinated use of all accessible technologies. IPM requires a systematic knowledge on crop biology and the biology of their pests and diseases, as well the existing plant protection procedures (Owen *et al.*, 2015).

In pesticide R&D the phenotype approach changed with the accumulation of knowledge in biochemistry and molecular biology, and research shifted toward a target-based one in order to take advantage of various new technologies, such as next-generation sequencing, transcriptomics, metabolomics, and proteomics. These methods are known to generate a huge number of data ("big data"), the interpretation of which is a new challenge for science.

Up until very recently, mining of the "big data" generated by the so-called "-omics" methods did not lead to breathtaking results: the number of new pesticide active

ingredients has been declining continuously. A recent announcement by Syngenta, the largest pesticide manufacturer in the world, indicates that this evident trend may change in the near future: the company has *ca.* 50 new crop protection innovations in the U.S. pipeline, including 19 new active ingredients (Syngenta, News Release on March 30, 2016). These numbers are remarkably high, well in the range in the “golden era” of the industry - even if only a fraction of the new active ingredients in the pipeline will actually reach commercialization. Still, it is very worrisome that discovery of compounds characterized with a new biochemical mode of action has been extremely rare during the last decades.

Nevertheless, the current R&D approach served well the largest chemical companies: they managed to increase their market share by mergers and acquisitions (*cf.* the merger of Dow Chemical and DuPont as well as Monsanto’s and ChemChina’s recent multibillion dollar bids to take over Syngenta) (Kaskey, 2015). Other negative consequence of the current prevalence of Eroom’s Law in pesticide R&D is that today generic products account for 70% of the pesticide market share. Needless to say, this situation is detrimental in many ways: it hurts not only the producers, but also the users who have to deal with the reoccurrence of pest resistance, and even the environment suffers from the accumulation of overused old compounds.

Now, is there a “chemical” way out? In my opinion there are two interesting paths to be explored.

(1) Designing pesticides that fit in the concept of “ecological plant protection” (EPP, coined in 1957: Nagy, 2008) – an almost 60 years old idea, preceding IPM with more than a decade. EPP is a close analogy to the recently introduced “systems biology” approach in the R&D and practical use of pharmaceuticals. Unfortunately, agro-ecosystems are so complex, that there are no “big data” systems developed yet for their description. Still, the combination of the continuously increasing capacity of data collection (and evaluation, *cf.* Moore’s Law) with target site (“-omics”) pesticide R&D may bring us pleasant surprises in the near future.

(2) We should be aware of the “-omics” technologies opening new insights into the chemical kingdom of nature: plants and microorganisms produce hundreds of thousands of metabolites, many of them “designed” to be bioactive (*e.g.*, for signal and defense). These may be major sources for new pesticides.

In addition, it is interesting to speculate on how the newly developed gene editing technology based on CRISPR (clustered regularly interspaced short palindromic repeats)–Cas (CRISPR-associated protein) systems can serve the chemical plant protection by

(1) reversing pesticide resistance in insects and weeds (*n.b.*, this may change agro-ecosystems), and
(2) increasing the production of natural pesticides in plants (in addition to their known possible roles in

breeding stress-tolerant and disease-resistant crops) (Wright *et al.*, 2016).

In summary, in the light of the most recent developments, 2016 could be a most interesting year for chemical plant protection research and for the pesticide industry, as a whole.

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